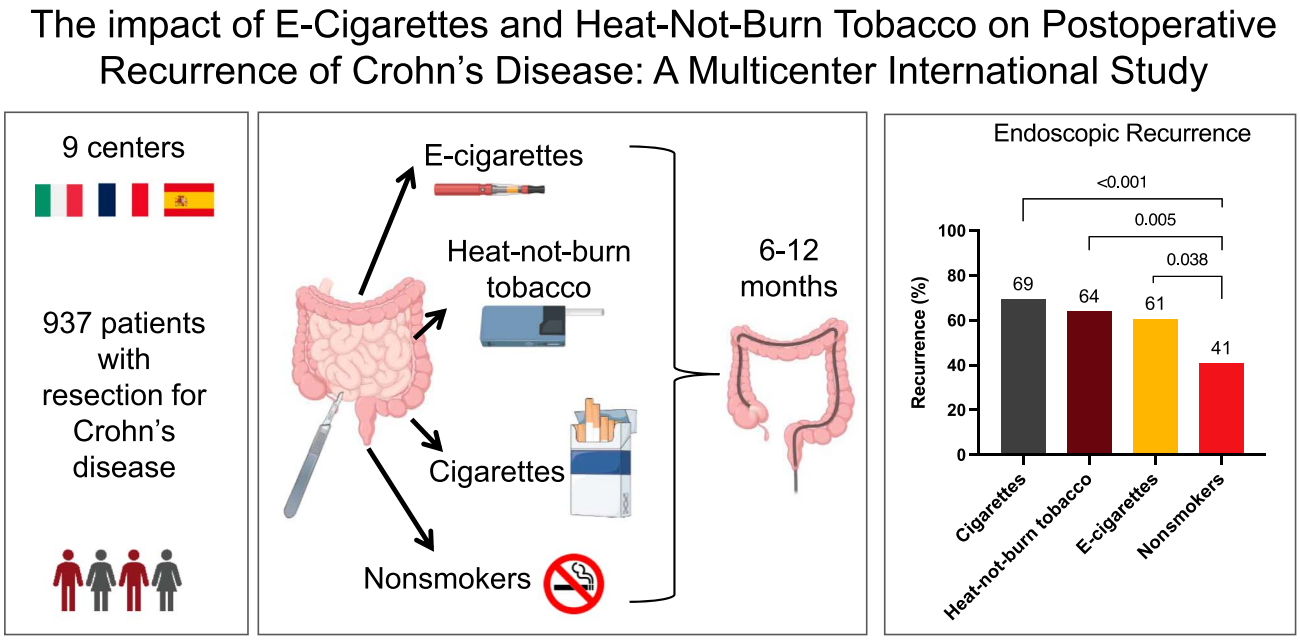
The Impact of E-Cigarettes and Heat-Not-Burn Tobacco on Postoperative Recurrence of Crohn's Disease: A Multicenter International Study

Tommaso Lorenzo Parigi, MD[1,2,3], Olga Maria Nardone, MD, PhD[4,5], Maria Lisa, MD[2], Luca Massimino, PhD[1], Roberto Gabbiadini, MD[6], Tommaso Innocenti, MD[7,8], Lorenzo Bertani, MD, PhD[9], Angelo Del Gaudio, MD[10,11], Pablo Florez, MD[12], Luisa Bertin, MD[13,14], Brigida Barberio, MD, PhD[13,14], Marianne Hupé, MD[15], Loris Lopetuso, MD, PhD[11,16], Mariangela Allocca, MD, PhD[1], Ferdinando D'Amico, MD, PhD[1], Federica Furfaro, MD, PhD[1], Alessandra Zilli, MD[1], Gionata Fiorino, MD, PhD[17], Federica Ungaro, PhD[1], Fabiana Castiglione, MD, PhD[4,5], Edoardo Savarino, MD, PhD[13,14], Gabriele Dragoni, MD, PhD[7,8], Franco Scaldaferri, MD, PhD[10,11], Alessandro Armuzzi, MD, PhD[6,18], Laurent Peyrin-Biroulet, MD, PhD[19], Vipul Jairath, MD, PhD[20], Theresa T. Pizarro, PhD[3] and Silvio Danese, MD, PhD[1,2]



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[1]Department of Gastroenterology, IRCCS Ospedale San Raffaele, Milan, Italy; [2]Università Vita Salute San Raffaele, Milan, Italy; [3]Department of Pathology, Case Western Reserve University, Cleveland, USA; [4]Department of Clinical Medicine and Surgery, Azienda Ospedaliera Universitaria Federico II, Naples, Italy; [5]Department of Public Health, University of Naples Federico II, Naples, Italy; [6]Department of Gastroenterology, IRCCS Humanitas Research Hospital, Milan, Italy; [7]Department of Gastroenterology, Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [8]Department of Experimental and Clinical Biochemical Sciences "Mario Serio," Università di Firenze, Florence, Italy; [9]Department of Internal Medicine, Tuscany North West ASL–Pontedera Hospital, Pontedera (PI), Italy; [10]Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [11]IBD UNIT-CEMAD, Medicina Interna e Gastroenterologia, Fondazione Policlinico A. Gemelli IRCCS, Roma, Italy; [12]Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain; [13]Department of Gastroenterology, Azienda Ospedale Università, Padova, Italy; [14]Department of Surgery, Oncology and Gastroenterology, Università di Padova, Padova, Italy; [15]Department of Gastroenterology, CHU Grenoble Alpes, Grenoble, France; [16]Dipartimento di Scienze della Vita, della Salute e delle Professioni Sanitarie, Link Campus University, Rome, Italy; [17]Department of Gastroenterology, ASL San Camillo Forlanini, Rome, Italy; [18]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [19]INFINY Institute, Department of Gastroenterology, CHRU Nancy, INSERM NGERE, Université de Lorraine, Vandœuvre-lès-Nancy, France; [20]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada. **Correspondence:** Tommaso Lorenzo Parigi, MD. E-mail: parigi.tommaso@hsr.it.

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INTRODUCTION: **Tobacco smoke is an established risk factor of Crohn's disease (CD) postoperative recurrence; however, the effect of e-cigarettes and heat-not-burn tobacco (HNBT) remains unknown. We aimed to evaluate the impact of e-cigarettes and HNBT on postoperative recurrence in patients with CD.**

METHODS: **We retrospectively included consecutive patients with CD who underwent ileocolic resection and endoscopic evaluation within 1 year across 9 centers in Italy, Spain, and France. Based on smoking habits between surgery and endoscopy, patients were categorized as nonsmokers, cigarette smokers, HNBT users, or e-cigarette users. Those using multiple products were excluded. The primary outcome was endoscopic recurrence (Rutgeerts score ≥2) 1 year after surgery. Secondary analyses included modified Rutgeerts score (≥i2b), mean Rutgeerts score, transmural disease activity, fecal calprotectin, time from diagnosis to surgery, and uni- and multivariable regression analysis.**

RESULTS: **Nine hundred thirty-seven patients were included, of which 691 (74%) were nonsmokers, 176 (19%) conventional cigarette smokers, 37 (4%) HNBT users, and 33 (4%) e-cigarette users. Recurrence rates were significantly higher in all smoking groups compared with nonsmokers (69.4%, 63.9%, and 60.6% for traditional cigarette, HNBT, and e-cigarette users, respectively, vs 40.8% for non-smokers; all $P < 0.05$). The association was also observed in patients receiving pharmacological prophylaxis, using the modified Rutgeerts score cutoff of i2b, mean Rutgeerts score, and fecal calprotectin levels. In multivariable regression analysis, HNBT use remained significantly associated with recurrence (odds ratio [OR] 2.76), whereas the association for e-cigarette missed statistical significance (OR 2.02, $P = 0.067$).**

DISCUSSION: **HNBT, and possibly e-cigarettes, are associated with increased endoscopic recurrence of CD compared with nonsmoking.**

KEYWORDS: e-cigarettes; heat-not-burn tobacco; smoke; Crohn's disease; postoperative

ABBREVIATION: B2, Stricturing behavior (Montreal classification); B3, Penetrating behavior (Montreal classification); CD, Crohn's disease; CDC, U.S. Centers for Disease Control and Prevention; CET, Comitato Etico Territoriale (Italian for Local Ethics Committee); CI, Confidence interval; CT, Computed tomography; E-cigarettes / e-cigarettes, Electronic cigarettes; HNBT, Heat-not-burn tobacco; ICD, International Classification of Diseases; L1, Ileal disease location (Montreal classification); L2, Colonic disease location (Montreal classification); L3, Ileocolonic disease location (Montreal classification); L4, Upper GI disease location (Montreal classification); MRE, Magnetic resonance enterography; NCT, National Clinical Trial identifier; OR, Odds ratio; POR, Postoperative disease recurrence; SD, Standard deviation; SES-CD, Simplified Endoscopic Score for Crohn's Disease; U.S., United States

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D807, http://links.lww.com/AJG/D808

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INTRODUCTION

Up to 50% of patients with Crohn's disease (CD) develop fibrostenotic and penetrating complications that require surgical resection, and around 70% of these patients suffer from a postoperative disease recurrence (POR) in the first year after intervention (1). Tobacco is the most established and the only modifiable risk factor of POR (2–6), roughly doubling its probability (7). Although the optimal strategy to prevent POR remains debated, the presence of risk factors, particularly smoking, is considered by many scientific guidelines as an indication to start prophylactic immunosuppressive treatment immediately after surgery before POR develops (8–11).

Over the last 2 decades, new smoking habits have emerged and gained popularity. E-cigarettes, short for electronic cigarettes, deliver an aerosol (commonly called vapor) by heating a solution usually containing propylene glycol or glycerol, flavoring agents, and typically nicotine. Even more recently, heat-not-burn tobacco products (HNBT) (e.g., IQOS) have appeared on the market in several countries. HNBT products are packaged similarly to short traditional cigarettes, contain tobacco soaked in propylene glycol, and are electrically heated to 250–350 °C in the dispensing device to release chemicals, including nicotine. Both types of products are marketed as healthier alternatives to traditional cigarettes, with fewer restrictions on their indoor use (12–14). Younger generations are among the greatest consumers of these new products (15). According to the US Center for Diseases Control and Prevention, 14% of American high-school students reported e-cigarettes use in the previous 30 days (16) in 2022, and around 6.5% of adult population reported current use in 2023, up from 3.7% in 2020 (17). The use of HNBT varies widely across regions, largely due to differences in regulatory policies and the evolving stage of market penetration. Although comprehensive aggregate data are lacking, market share figures can serve as a proxy. In 2023, the leading HNBT brand accounted for approximately 10.6% of total tobacco sales in Europe, with an even higher market share of 17% in Italy (18,19).

As e-cigarettes and HNBT differ from conventional tobacco cigarettes in composition, combustion, and released chemicals, and considering their increasing popularity, it is essential to determine whether they also carry risks of POR. Therefore, to fill

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this knowledge gap and provide empirical clinical data to guide the management of patients with CD who use e-cigarettes and HNBT, a retrospective study was conducted to investigate the impact of such products on POR in CD.

METHODS

Inclusion

A multicenter retrospective study was conducted across 9 centers in Italy, Spain, and France. Consecutive patients with an established diagnosis of CD who underwent ileocolic resection between January 2010 and April 2024 due to active or complicated CD, followed by endoscopic re-evaluation 6–12 months post-surgery, were included. Medical records from the immediate postoperative period were reviewed for information on smoking habits. Smoking status was categorized as follows: nonsmokers, e-cigarette users, HNBT users (e.g., IQOS), and traditional tobacco cigarette users.

To reduce confounding, we excluded patients with changes in smoking behavior during the postoperative period (e.g., patients who quit smoking or switched from cigarettes to e-cigarettes), those who used multiple products concurrently (e.g., both e-cigarettes and traditional cigarettes), those with missing or inconsistent smoking data in the medical records, and those who smoked cannabis or cigars. To verify exclusive use of e-cigarettes or HNBT, users of either product were asked to confirm their usage through phone calls or during outpatient clinic visits.

Outcomes

The primary outcome was endoscopic recurrence, defined as a Rutgeerts Score ≥2 within the first year after surgery (20). A secondary analysis was conducted using the modified Rutgeerts Score, defining recurrence as a score ≥i2b, when available or attributable based on the endoscopic report. In addition, to capture the full range of endoscopic activity, and considering that Simplified Endoscopic Score for CD is often not reported and less reliable in patient who underwent resection, we used the mean Rutgeerts score as a continuous variable. To do so, we assigned numerical values to each Rutgeerts category (0 = 0, i1 = 1, i2 = 2, i3 = 3, i4 = 4). In addition, if intestinal ultrasound or imaging assessment was available at the time of endoscopy (±2 months), transmural activity was recorded. For intestinal ultrasound, activity was defined as a bowel wall thickening greater than 3 mm with increased color doppler signal, whereas for computed tomography and magnetic resonance enterography, inflammatory activity was retrieved from the scan report (21). Similarly, levels of fecal calprotectin at the time of endoscopy (±2 months) were recorded when available, and biochemical activity was defined as calprotectin ≥150 μg/g. Postoperative prophylaxis was defined as a prescription of any approved biologic or azathioprine within 2 months from surgery.

Statistical analysis

Differences in recurrence rates were analyzed using the Fisher exact test, with pairwise comparisons adjusted through Bonferroni correction. The mean endoscopic scores across groups were compared using Kruskal-Wallis tests, followed by Dunn test for pairwise comparisons. Continuous and categorical clinical variables were compared with respect to nonsmokers by Welch t test and χ^2 test, respectively, using Prism GraphPad (San Diego, CA). Univariable and multivariable regression analyses were used to calculate odds ratios (ORs), produced with finalfit R package (https://github.com/ewenharrison/finalfit). A 2-sided P value of < 0.05 indicated statistical significance. Ethics approval for Italian centers was obtained from Comitato Etico Territoriale Lombardia 1 (CET 419-2024), whereas Spanish and French centers obtained approval from their local institutional review boards. The study is registered on clinicaltrials.gov (NCT 06734780).

RESULTS

Patients

In total, 1,113 patients were screened. After excluding patients who had colonoscopy out of the prespecified time window (6–12 months after operation) (n = 145), those smoking multiple products (n = 28), and cannabis users (n = 3), we included 937 patients (see Supplementary Figure 1, http://links.lww.com/AJG/D808). Most patients were male (59.1% or 554) with a mean age at the time of surgery of 42.0 years (SD 15.8) and a mean disease duration of 8.9 years (SD 9.2). At the time of diagnosis, CD was primarily localized in the ileum (L1, 48.9%) or in the ileum and colon (L3, 43.7%) and presented with mostly stricturing (B2, 44.4%) or penetrating (B3, 38.5%) behavior. A minority of patients were initially classified as having isolated colonic disease (L2, 5.7%) or upper gastrointestinal involvement (L4, 0.5%); however, all of these patients subsequently developed ileal or ileocecal valve involvement and underwent ileocecal resection. Nonsmokers comprised the largest group (n = 691), followed by conventional cigarette smokers (n = 176), HNBT users (n = 37), and e-cigarette users (n = 33). The groups were homogeneous regarding sex, history of intestinal surgery due to CD, and prescription of POR prophylaxis. On the contrary, e-cigarette and HNBT users were younger than nonsmokers (35.3 and 32.6 vs 42.5; $P = 0.05$ and $P < 0.01$). Demographic and clinical characteristics are detailed in Table 1.

Primary outcome

For the primary analysis of endoscopic POR at 1 year, a Rutgeerts score was available for 760 patients (81.1%). The rates of recurrence (Rutgeerts Score ≥2) within the first year after surgery were significantly higher in all smoking groups compared with nonsmokers (69.4%, 63.9%, and 60.6%, for conventional cigarettes, HNBT, and e-cigarettes, respectively, vs 40.8% among nonsmokers, all $P < 0.05$) (Figure 1a). When restricting the analysis to patients who received postoperative prophylactic therapy with azathioprine or biologics initiated within 2 months after surgery, recurrence rates remained approximately similar: 70.0%, 66.7%, 63.0%, and 41.6% for the same groups, with all comparisons retaining statistical significance (all $P < 0.05$) (Figure 1b).

Secondary outcomes

Modified Rutgeerts score. As the clinical relevance of mucosal inflammation limited to the anastomosis remains debated, a secondary analysis was performed using the more stringent cutoff for recurrence of modified Rutgeerts score ≥2b. This distinction allows differentiation between patients with inflammation in the neoterminal ileum (2b) or limited to the anastomosis (2a). As expected, raising the cutoff decreased overall recurrence rates, specifically to 54.9% for conventional cigarette, 52.8% for HNBT users, 51.5% for e-cigarette users, and 33.1% for nonsmokers. However, the relative proportions remained consistent, and the

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Table 1. Demographics and clinical characteristics

	Total	Non-smokers	Cigarette smokers	*P* value	E-cigarette smokers	*P* value	Heat-not-burn tobacco smokers	*P* value
Number	937 (100)	691 (73.7)	176 (18.8)		33 (3.5)		37 (4.0)	
Male (%)	554 (59.1)	405 (58.6)	106 (60.2)	0.73	22 (66.7)	0.35	20 (54.1)	0.49
Age at surgery (SD)	42.0 (15.8)	42.5 (16.1)	43.1 (14.6)	0.99	35.3 (13.9)	**0.05**	32.6 (11.9)	**<0.01**
Disease duration at time of surgery (SD)	8.9 (9.2)	9.4 (9.4)	8.0 (8.8)	**<0.01**	6.9 (8.1)	0.29	5.8 (4.7)	**0.04**
Prior intestinal resection due to CD (%)	158 (16.8)	115 (16.6)	33 (18.8)	0.50	6 (18.2)	0.81	4 (11.1)	0.35
Biologics before surgery (%)	696 (74.3)	530 (76.7)	123 (69.9)	0.06	22 (66.7)	0.18	21 (56.8)	**<0.01**
POR prophylaxis (%)	759 (81.0)	553 (80.0)	145 (82.4)	0.48	27 (81.8)	0.80	34 (91.8)	0.08
AZA	125 (13.3)	101 (14.6)	20 (11.4)		2 (6.0)		2 (5.4)	
Anti-TNF	475 (50.7)	333 (48.2)	92 (52.3)		21 (63.6)		29 (78.4)	
VEDO	57 (6.1)	45 (6.5)	11 (6.3)		0		1 (2.7)	
USTE	88 (9.4)	62 (9.0)	20 (11.4)		4 (12.1)		2 (5.4)	
Other	14 (1.5)	12 (1.7)	2 (1.1)		0		0	
Location at diagnosis (%)								
L1	459 (48.9)	341 (49.3)	89 (50.6)		14 (42.4)		14 (37.8)	
L2	53 (5.7)	46 (6.7)	5 (2.8)				2 (5.4)	
L3	409 (43.7)	293 (42.4)	77 (43.8)		19 (57.6)		20 (54.1)	
L4	5 (0.5)	4 (0.6)	1 (0.6)					
L1 + L4	6 (0.6)	3 (0.4)	3 (1.7)					
L1 + L4	5 (0.5)	3 (0.4)	1 (0.6)				1 (2.7)	
Behavior at diagnosis (%)								
B1	160 (17.1)	117 (16.9)	29 (16.5)		6 (16.7)		8 (21.6)	
B2	416 (44.4)	300 (43.4)	81 (46.0)		18 (50.0)		17 (45.9)	
B3	361 (38.5)	274 (39.7)	66 (37.5)		9 (25.0)		12 (32.4)	
Type of anastomosis (%)								
Side-to-Side	704 (75.1)	528 (76.4)	126 (71.6)		21 (58.3)		29 (78.4)	
End-to-Side	46 (4.9)	32 (4.6)	11 (6.3)		2 (5.6)		1 (2.7)	
End-to-End	23 (2.5)	16 (2.3)	5 (2.8)		0		2 (5.4)	
Kono-S	13 (1.4)	10 (1.5)	1 (0.6)		1 (2.8)		1 (2.7)	
Other	3 (0.3)	1	2 (1.1)		0		0	
NA	148 (15.8)	104 (15.1)	31 (17.6)		9 (25.0)		4 (10.8)	

P values refer to comparison with nonsmokers and are calculated with Welch *t* test of continuous variables and with χ^2 test for categorical variables. In bold, statistically significant *P* values.
AZA, azathioprine; NA, not available; POR, postoperative recurrence; USTE, ustekinumab; VEDO, vedolizumab.

differences between groups did not change (see Supplementary Figure 2A, http://links.lww.com/AJG/D808).

Mean endoscopic activity. When analyzing the Rutgeerts score as a continuous variable, traditional cigarette smoking, HNBT use, and e-cigarette use continued to be associated with significantly greater endoscopic disease activity compared with nonsmokers (2.08, 1.97, and 1.76, respectively, vs 1.18; all $P < 0.05$) (Figure 2a). Interestingly, the mean Rutgeerts score among e-cigarette users was lower than that of conventional tobacco cigarettes and HNBT although the difference was not statistically significant (1.76 vs 2.08, $P > 0.05$).

Biochemical activity. The analysis of biochemical activity, defined as fecal calprotectin level ≥150 (μg/g) at the time of colonoscopy (±2 months), confirmed the trends observed for endoscopy. In particular, 64.6%, 53.9%, and 46.2% of traditional cigarettes smokers, HNBT, and e-cigarette users, respectively, had biochemical activity compared with 26.3% of nonsmokers (all comparisons $P < 0.05$) (Figure 2b). A similar trend was observed for mean calprotectin levels (300, 264, and 185 μg/g for the same groups, vs 120 μg/g in nonsmokers) (see Supplementary Figure 2B, http://links.lww.com/AJG/D808).

Transmural activity. Transmural activity at the time of endoscopy (±2 months), was observed in 59.4%, 50.0%, and 44.4% of traditional cigarette smokers, HNBT, and e-cigarette users, respectively, compared with 40.0% of nonsmokers. For this analysis, the only significant comparison was between conventional smokers and nonsmokers ($P < 0.001$), while differences of HNBT and e-cigarettes with nonsmokers did not reach statistical

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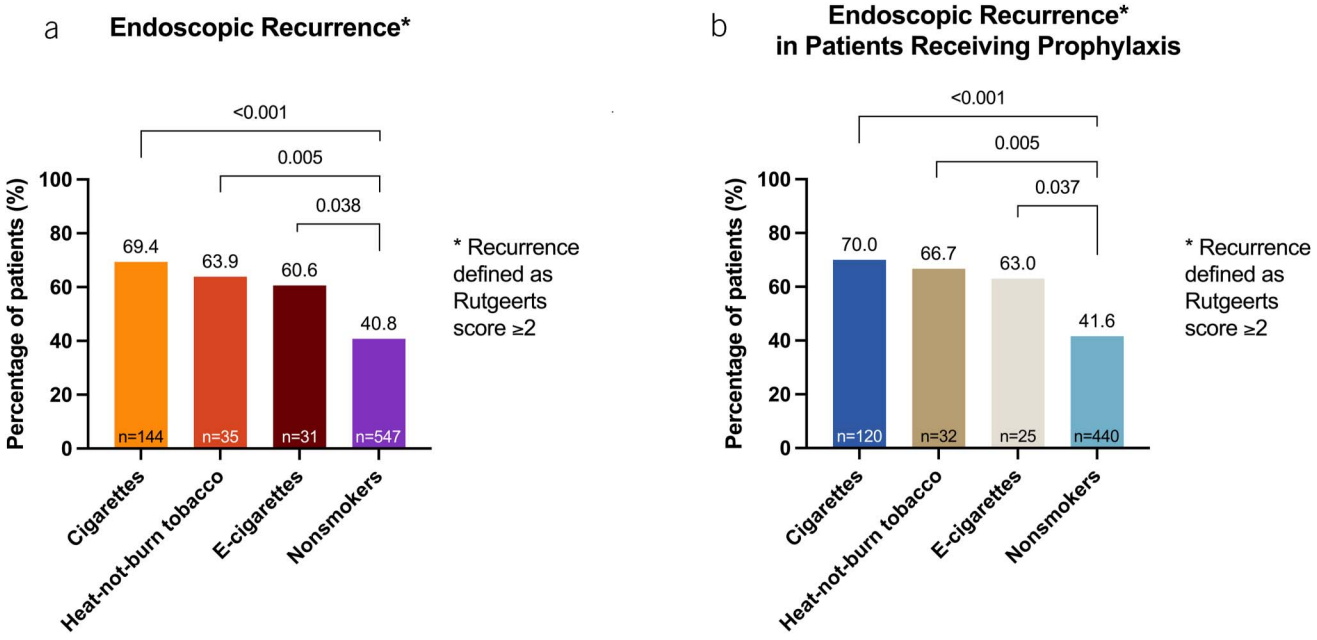

Figure 1. Rates of endoscopic recurrence 1 year after surgery per smoking group. (**a, b**) Rates of endoscopic recurrence defined as a Rutgeerts score ≥2 in whole cohort (**a**) and patients receiving prophylaxis (**b**).

significance, possibly due to the limited availability of these data (Figure 2c).

Multivariable regression analysis. To adjust for potential confounders and determine the independent effect of each factor, we first conducted univariable regression analyses to assess the association between individual clinical variables and the risk of postoperative recurrence. Variables that demonstrated statistical significance in the univariable analyses were subsequently included in a multivariable regression model to identify independent predictors of recurrence. At univariable regression analysis, sex, disease location at diagnosis, behavior at diagnosis, presence of perianal disease, disease duration at time of surgery, age at surgery, type of anastomosis, previous intestinal resection(s) due to CD, prophylaxis and smoking habits after surgery were assessed. Individual results of the univariable and multivariable regression are summarized in Supplementary Digital Content (see Supplementary Table 1, http://links.lww.com/AJG/D807). At multivariable analysis, traditional cigarettes and HNBT remained

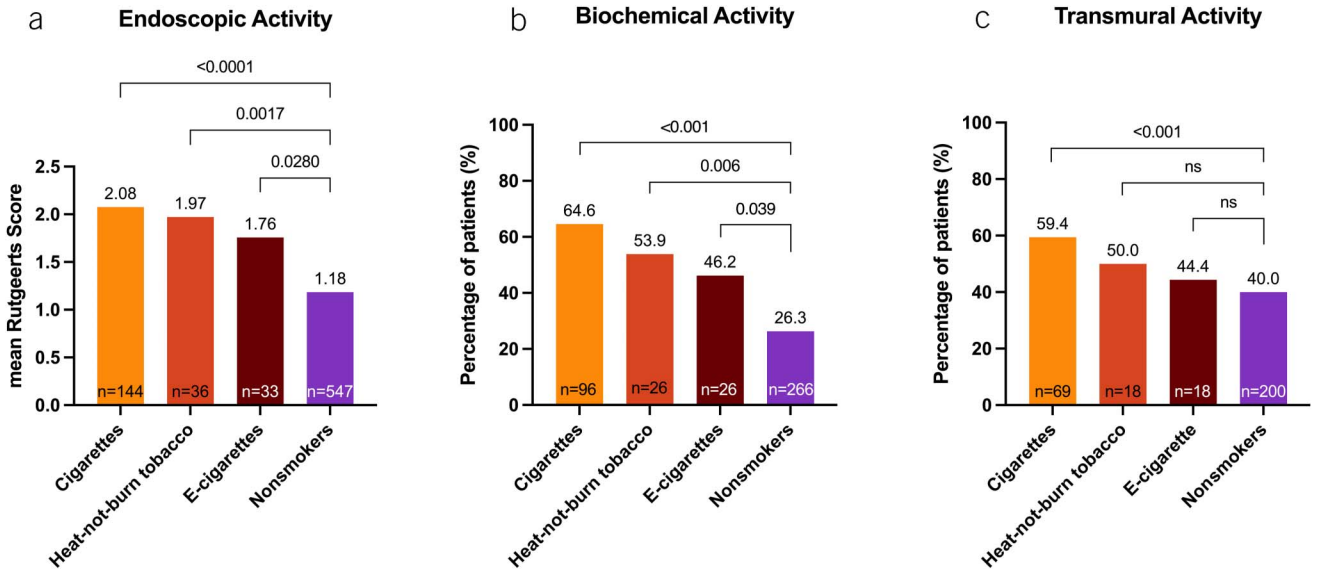

Figure 2. Additional measures of disease activity 1 year after surgery. (**a**) Mean Rutgeerts score (calculated assigning numerical values to each Rutgeerts category: 0 = 0, i1 = 1, i2 = 2, i3 = 3, i4 = 4); (**b**) proportion of patients with biochemical activity defined as fecal calprotectin levels at the time of endoscopy (±2 months) ≥ 150 mcg/g; (**c**) proportion of patients with radiologic evidence of transmural activity at the time of endoscopy (±2 months). Transmural activity was defined for intestinal ultrasound as a thickening of the bowel wall ≥3 mm combined with an increased color doppler signal or in the case of magnetic resonance and computed tomography scan, as described in the imaging report.

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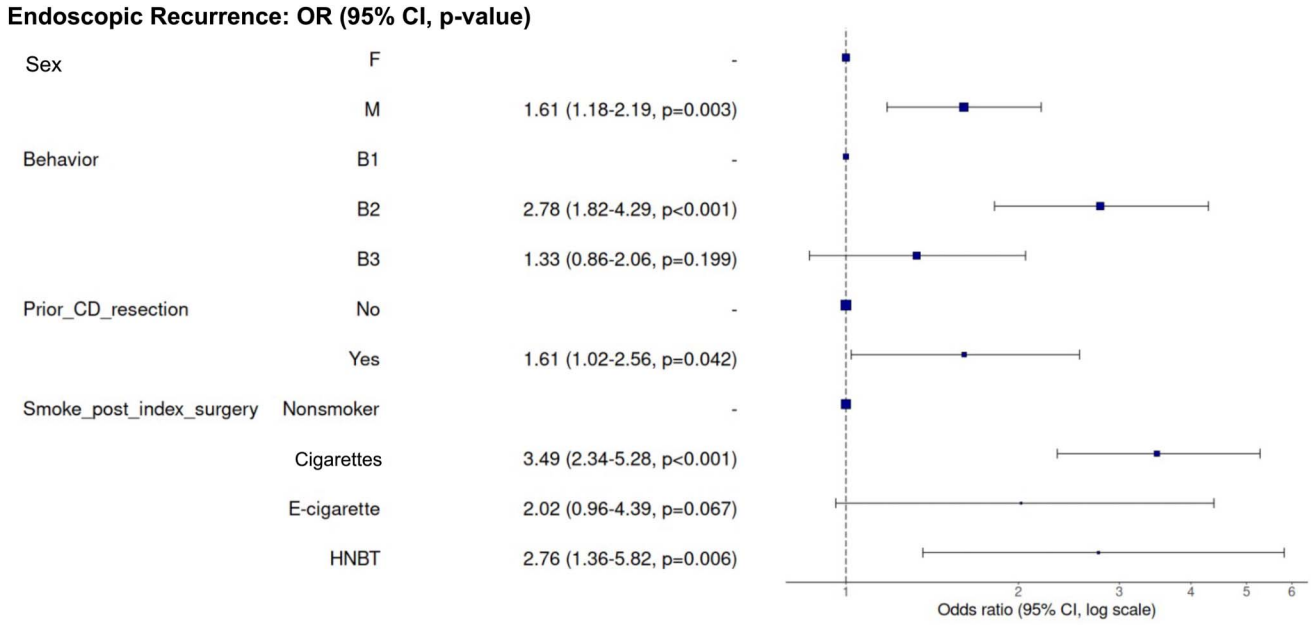

Figure 3. Multivariable regression analysis. Tradition cigarettes and HNBT remained significantly associated with endoscopic recurrence (Rutgeerts score >2) even after accounting for multiple possible confounders; instead, e-cigarette's association did not reach statistical significance ($P = 0.067$). In addition, male sex, stricturing disease at the time of diagnosis, and previous intestinal resections were also independently associated with endoscopic recurrence. B1, inflammatory; B2, stricturing; B3, penetrating; CD, Crohn's disease; F, female; HNBT, heat-not-burn tobacco; L1, Crohn's disease of the ileum; L2 Crohn's disease of the colon; L3, Crohn's disease of the ileum and colon; M, male.

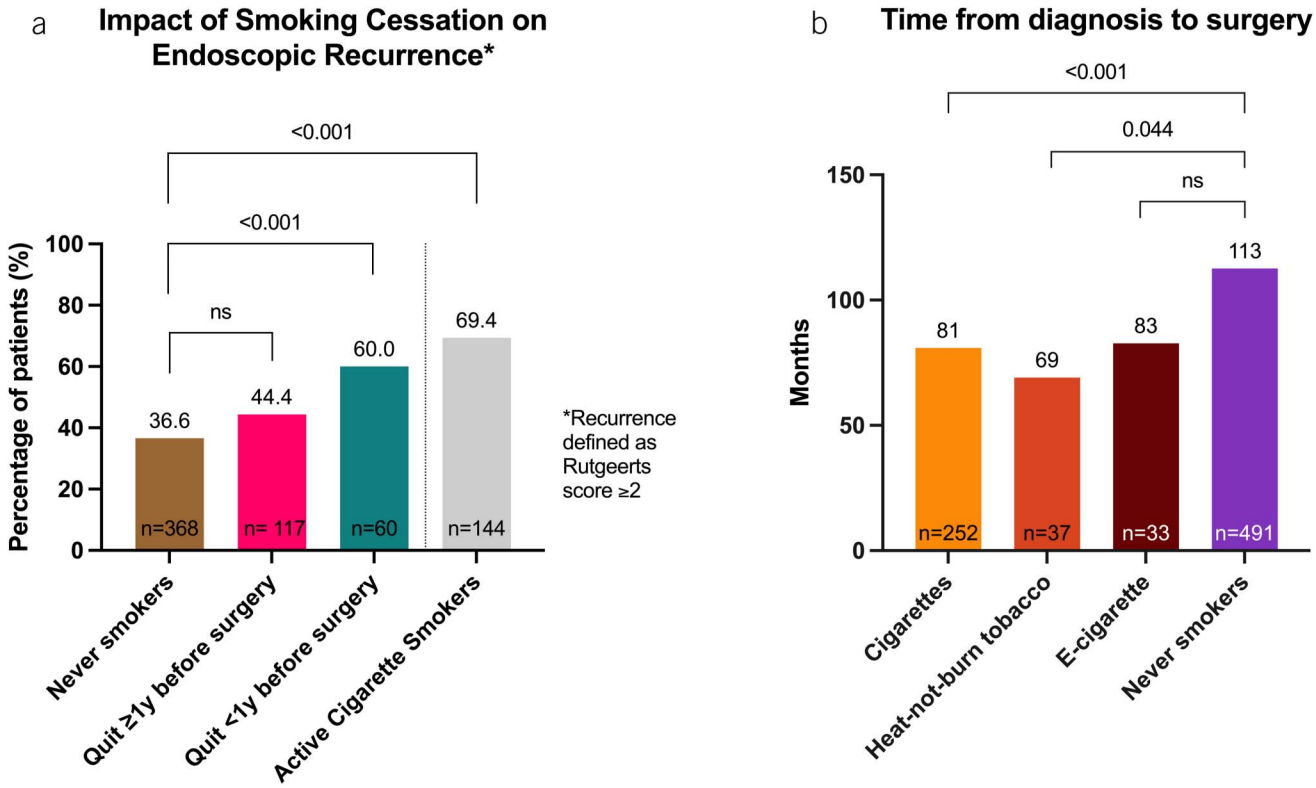

Figure 4. Impact of smoking and smoking cessation on disease course. (**a**) Duration of smoking impact on Crohn's disease recurrence after cessation. The negative impact normalizes after 1 year from cessation. (**b**) Association of different smoking habits on the time from diagnosis to surgery and indirect measure of the aggressiveness of the disease.

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significantly associated with endoscopic recurrence compared with nonsmokers (odds ratio [OR] 3.49, 95% confidence interval [CI] 2.34–5.28, $P < 0.001$ and OR 2.76, 95% CI 1.36–5.82, $P = 0.006$, respectively), whereas the association of e-cigarette did not reach statistical significance (2.02, 95% CI 0.96–4.39, $P = 0.067$), indicating a potential but unconfirmed association. Other independent predictors of recurrence were male sex (OR 1.61, 95% CI 1.18–2.19, $P = 0.003$), stricturing disease behavior at diagnosis (OR 2.78, 95% CI 1.82–4.29, $P < 0.001$), and previous intestinal resection due to CD (OR 1.61, 95% CI 1.02–2.56, $P = 0.042$) (Figure 3).

Impact of timing of smoking cessation on POR. Given the uncertainty about how long the detrimental effects of smoking persist after cessation, and considering that novel smoking products are often used in attempt to quit conventional cigarettes, we stratified nonsmoking patients for which endoscopic recurrence data were available (n = 547) into 3 subgroups: those who had never smoked (n = 368), those who quit at the time of surgery or in the preceding 12 months (n = 60), and those who quit more than 1 year before surgery (n = 117). Endoscopic recurrence (Rutgeerts ≥ i2) was less common in never-smokers (36.6%) and former smokers (44.4%) compared with those who quit in the year before surgery (60.0%; both $P < 0.01$). Instead, the difference between active smokers and recent quitters (69.4% vs 60.0%) did not reach statistical significance ($P = 0.19$) (Figure 4a).

Time to surgery. Restricting the analysis to patients with stable smoking patterns before surgery and excluding those who changed smoking products, we assessed disease durations at the time of surgery. Compared with those who never smoked, patients who smoked traditional cigarettes and used HNBT had a significantly shorter disease duration at the time of intervention (81 and 69 months vs 113; $P < 0.001$ and $P = 0.044$ respectively), suggestive of a more aggressive disease course. Instead, the difference with e-cigarette users was not significant (83 months, $P = 0.30$; Figure 4b).

DISCUSSION

Smoking tobacco is known to worsen the course of CD and increase the risk of recurrence after surgery (22,23). Over the past decade, e-cigarettes and HNBT have become popular alternatives to traditional cigarettes, especially among younger people. However, their effects on health are still largely unknown (16,24). In this first study on the impact of e-cigarettes and HNBT on CD POR, we find that HNBT, and possibly also e-cigarettes, are associated with an increased risk of endoscopic recurrence compared with nonsmoking. Importantly, these associations were maintained, irrespective of postoperative prophylaxis and the cutoff used for endoscopic recurrence. The secondary analyses, including the average endoscopic activity, proportion of patients with transmural activity, biochemical activity, and the mean levels of fecal calprotectin, all revealed a gradient of severity, highest among traditional cigarette smokers, followed by HNBT users, then e-cigarette users, and lowest among nonsmokers. The multivariable regression analysis, adjusting for potential confounders, confirmed the association with endoscopic recurrence only for traditional cigarette use (OR 3.49) and HNBT use (OR 2.76). While the OR for e-cigarette use was elevated (OR 2.02), it missed statistical significance ($P = 0.067$), indicating a potential but unconfirmed association.

Although e-cigarettes and HNBT have been available for over a decade, research on their health impact has been slowed by the difficulty in separating their effect from that of conventional cigarettes, since that most users are also active or former smokers. To address this, we strictly limited our inclusion to patients who were using only one type of product from the time of surgery to reassessment and confirmed use of e-cigarettes and HNBT through phone call or in-person visits. Furthermore, as smoking habits change over time so does the impact on disease. Because many e-cigarette and HNBT users are former tobacco smokers, we aimed to determine how long after quitting conventional smoking the risk of endoscopic POR returned to normal and, indirectly, whether this might have affected our findings. We observed that smoking cessation for more than 1 year is associated with similar, though not identical, recurrence rates as for patients who never smoked (44.4% vs 36.4%, $P = 0.16$), whereas cessation in the year preceding surgery still confers a significantly higher risk of recurrence (Δ 23% compared with never-smokers, $P < 0.001$). As 12% (n = 4) of e-cigarette users and 10% (n = 4) of HNBT smokers included in our study switched from conventional cigarettes to the respective product in the year before surgery, a carry-over effect from previous tobacco might have minimally affected our results. However, such proportions are small and are unlikely to have changed the conclusions. In addition, although not the primary focus of our study, these findings could help clinicians better estimate the postoperative risk in patients who quit smoking around the time of surgery.

Overall, our findings challenge the perception—often promoted in marketing (14)—that e-cigarettes and HNBT are safe. Instead, we observed a negative impact, albeit less severe for e-cigarettes, on disease course both after and before surgery. Our results differ from the only study on e-cigarette use in inflammatory bowel disease (IBD), which compares outcomes (based on *International Classification of Diseases* [*ICD*] codes) in 85 patients with CD, smoking e-cigarettes and nonvaping matched controls, and found no difference in biologic switch, hospitalization, or surgery (25). Various differences could explain the discrepancy in the conclusions, including the fact that nonvaping controls comprised both smokers and nonsmokers, assessment of broader outcomes, the reliance on *ICD* codes, and the high proportion (37%) of e-cigarette users who also smoked tobacco (instead, excluded from our study) all limit the comparison. In regard to HNBT, to the best of our knowledge, there are no published studies in the field of IBD or even gastroenterology; therefore, comparisons are not possible. Nevertheless, HNBT is reported to induce damage and proinflammatory changes in the lung similar to those elicited by conventional cigarettes (26), and increase cardiovascular risk (24); hence, a negative effect on intestinal inflammation is biologically plausible.

Our study has significant clinical implications, as smoking is the strongest risk factor of POR and a key determinant in deciding whether to initiate preventive therapy postoperatively. Based on our findings, we suggest that patients using e-cigarettes and HNBT should be managed with a similar level of caution as conventional smokers, with a low threshold for initiating prophylactic biologics (11). Furthermore, switching from traditional cigarettes to e-cigarettes and HNBT should not be viewed as a risk-free alternative. Instead, complete smoking cessation should remain the only recommended strategy, and even when this is achieved, the risk reduction may not be immediate.

The similarly negative effects of these distinct products raise important questions about the specific chemicals and pathways

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driving their inflammatory impact. Unfortunately, a definitive answer remains elusive even for conventional tobacco cigarettes, let alone newer products such as e-cigarettes and HNBT. However, at least speculatively, the detrimental effect on postoperative recurrence is unlikely to be driven by combustion (which is absent in both HNBT and e-cigarettes) or tobacco itself (which is absent in e-cigarettes) but rather by other common substances, such as for example nicotine. In line with this concept, when we restrict the analysis to the patients who received POR prophylaxis (n = 759 or 81%), recurrence rates remain nearly unchanged, suggesting that treatment modulates in a similar way the inflammatory effects the different smoking products.

The main limitation of our study is the relatively low number of patients using e-cigarettes and HNBT. However, these proportions are in line with the prevalence of e-cigarette and HNBT use in the countries where the study was conducted, especially when excluding mixed smokers, and considering that use of both e-cigarettes and HNBT has steadily increased in the period considered (2010–2024). Second, the use of e-cigarettes and HNBT might have been underreported in medical records, due to patients or physicians omitting this information, as it may not be perceived as relevant. Similarly, given the nonlegalized status of cannabis in the 3 participating countries and the associated social stigma, it is likely that more patients than the 3 we excluded were using cannabis, which could have acted as an additional confounder. Another limitation is the considerable heterogeneity in e-cigarette products (e.g., with or without glycerol, with or without nicotine, rechargeable vs disposable), which may influence exposure levels and the associated risk of recurrence. Finally, accurately quantifying e-cigarette consumption is more challenging than measuring traditional cigarette use and even for that data on pack/years was too fragmented to allow meaningful analysis. Despite these limitations, our findings challenge the notion of "safe" smoking alternatives.

In this first study that examines the impact of new smoking products on postoperative CD, HNBT, and possibly e-cigarettes was associated with a higher risk of endoscopic recurrence compared with nonsmoking. Based on these observations, we suggest that patients with CD using e-cigarettes or HNBT be managed similarly to traditional smokers in the postoperative setting.

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CONFLICTS OF INTEREST

Guarantor of the article: Tommaso Lorenzo Parigi, MD.

Specific author contributions: T.L.P.: conceptualization: lead; data curation: lead; formal analysis: lead; writing–original draft: lead. O.M.N.: conceptualization: equal; data curation: equal; writing–original draft: supporting. M.L.: data curation: equal; writing–review and editing: supporting. L.M.: formal analysis: equal; methodology: equal; writing–review and editing: equal. R.G.: data curation: equal; writing–review and editing: equal. T.I.: data curation: equal; writing–review and editing: equal. L.B.: data curation: equal; writing–review and editing: equal. A.D.G.: data curation: equal; writing–review and editing: equal. P.F.D.: data curation: equal; writing–review and editing: equal. L.B.: data curation: equal; writing–review and editing: equal. B.B.: data curation: equal; writing–review and editing: equal. M.H.: data curation: equal; writing–review and editing: equal. L.L.: data curation: equal; writing–review and editing: equal. M.A.: writing–review and editing: equal. F.D'A.: writing–review and editing: equal. F.F.: writing–review and editing: equal. A.Z.: writing–review and editing: equal. G.F.: writing–review and editing: equal. F.U.: writing–review and editing: equal. F.C.: writing–review and editing: equal. E.S.: writing–review and editing: equal. G.D.: data curation: equal; writing–review and editing: equal. F.S.: writing–review and editing: equal. A.A.: writing–review and editing: equal. L.P.-B.: writing–review and editing: equal. V.J.: writing–review and editing: equal. T.T.P.: writing–review and editing: equal. S.D.: writing–review and editing: equal. All authors reviewed and approved the final version of the manuscript.

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Data availability: Made available upon reasonable request to the corresponding author.

Study Highlights

WHAT IS KNOWN

- ✓ Smoking is a key risk factor for postoperative recurrence of Crohn's disease.
- ✓ The impact of e-cigarettes and heat-not-burn tobacco on Crohn's postoperative recurrence is unknown.

WHAT IS NEW HERE

- ✓ Use of heat-not-burn tobacco was significantly associated with an increased risk of endoscopic postoperative recurrence.
- ✓ Use of e-cigarette was associated with increased risk of postoperative recurrence in unadjusted and most secondary analyses, though not statistically significant in multivariable analysis.

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